

## Evaluation of procalcitonin, interleukin 6, and tumor necrosis factor alpha levels as early markers of postoperative complications following major thoracic surgery

*Majör torasik cerrahi sonrası komplikasyonların erken belirteçleri olarak prokalsitonin, interlökin 6 ve tümör nekroz faktör alfanın değerlendirilmesi*

Hıdır Esmе,<sup>1</sup> Burhan Apilioğulları,<sup>1</sup> Recep Keşli,<sup>2</sup> Banu Yoldaş,<sup>1</sup> Taha Bekçi,<sup>3</sup> Mustafa Çalık<sup>2</sup>

<sup>1</sup>Department of Thoracic Surgery, Konya Training and Research Hospital, Konya, Turkey;

<sup>2</sup>Department of Microbiology, Konya Training and Research Hospital, Konya, Turkey;

<sup>3</sup>Department of Chest Diseases, Konya Training and Research Hospital, Konya, Turkey

**Background:** This prospective study aims to investigate the association between systemic inflammation and risk for postoperative complications in patients undergoing major thoracic surgery.

**Methods:** Thirty-seven patients (23 males, 14 females; mean age 53.9 years; range 44 to 72 years) undergoing thoracotomy for lung resection were included. Serum procalcitonin, interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF- $\alpha$ ) concentrations were measured at baseline and on the first, fifth and seventh day following surgery. Demographic data, reasons for thoracotomy, type of lung resection, duration of surgery, length of hospital stay, and postoperative complications were recorded.

**Results:** Serum concentrations of procalcitonin, IL-6, and TNF- $\alpha$  after surgery were significantly higher compared to the preoperative values. Patients with postoperative complications had approximately a three-fold elevation in procalcitonin levels at postoperative days one and five, and a two-fold elevation in IL-6 levels at postoperative day seven, compared to patients without pulmonary complications. The procalcitonin levels on postoperative days one and five and IL-6 levels on postoperative day seven were significantly different between the groups with and without postoperative complications.

**Conclusion:** An elevated procalcitonin level on postoperative day one is a promising early marker of postoperative complications. Elevated concentrations of procalcitonin, IL-6, and TNF- $\alpha$  in the postoperative period are markers of the severity of surgical injury. These findings may contribute to alert us and make further examinations.

**Key words:** Complications; interleukin 6; procalcitonin; thoracic surgery; tumor necrosis factor alpha.

**Amaç:** Bu prospektif çalışmada majör göğüs cerrahisi uygulanan hastalarda ameliyat sonrası komplikasyon riski ile sistemik inflamasyon arasındaki birliktelik araştırıldı.

**Çalışma planı:** Akciğer rezeksiyonu için torakotomi uygulanan 37 hasta (23 erkek, 14 kadın; ort yaş 53.9 yıl; dağılım 44-72 yıl) çalışmaya dahil edildi. Serum prokalsitonin, interlökin 6 (IL-6) ve tümör nekroz faktör alfa (TNF- $\alpha$ ) konsantrasyonları cerrahi öncesi ve cerrahi sonrası bir, beş ve yedinci günlerde ölçüldü. Demografik bilgiler, torakotomi nedenleri, akciğer rezeksiyon tipi, ameliyat süresi, hastanede kalış süresi ve ameliyat sonrası komplikasyonlar kaydedildi.

**Bulgular:** Ameliyat sonrası serum prokalsitonin, IL-6 ve TNF- $\alpha$  konsantrasyonları ameliyat öncesi değerler ile karşılaştırıldığında anlamlı olarak daha yüksek idi. Ameliyat sonrası komplikasyonlu hastalar, komplikasyon gelişmeyen hastalar ile karşılaştırıldığında ameliyat sonrası bir ve beşinci günlerde prokalsitonin seviyesi yaklaşık üç kat, ameliyat sonrası yedinci gün IL-6 seviyesi iki kat yüksek idi. Ameliyat sonrası bir ve beşinci günlerde prokalsitonin, ameliyat sonrası yedinci gün IL-6 düzeylerinde, ameliyat sonrası komplikasyon olan ve olmayan gruplar arasında anlamlı fark vardı.

**Sonuç:** Ameliyat sonrası birinci gün yükselmiş prokalsitonin seviyesi ameliyat sonrası komplikasyonların ümit verici erken bir göstergesidir. Ameliyat sonrası dönemde prokalsitonin, IL-6 ve TNF- $\alpha$  konsantrasyonlarının yükselmesi cerrahi travmanın ciddiyetinin göstergesidir. Bu bulgular tetikte olmamızı ve ileri incelemelerde bulunmamıza yardımcı olabilir.

**Anahtar sözcükler:** Komplikasyonlar; interlökin 6; prokalsitonin; torasik cerrahi; tümör nekroz faktör alfa.



Available online at  
www.tgkdc.dergisi.org  
doi: 10.5606/tgkdc.dergisi.2012.166  
QR (Quick Response) Code

Received: November 25, 2011 Accepted: April 16, 2012

Correspondence: Hıdır Esmе, M.D. Konya Eğitim ve Araştırma Hastanesi, Göğüs Cerrahisi Kliniği, 42040 Meram, Konya, Turkey.

Tel: +90 505 - 812 93 78 e-mail: drhesme@hotmail.com

Thoracotomies for lung resection are one of the most invasive surgical procedures and are associated with a high rate of postoperative complications and extended hospital stays necessitating higher costs. Over 30% of patients develop life-threatening complications, such as pulmonary infections, cardiac arrhythmias, and atelectasis requiring bronchoaspiration after anatomic lung resections, with this surgical procedure.<sup>[1]</sup> In addition, in most specialized centers, the mortality rate after lobectomies is near 2%.<sup>[2,3]</sup> The ability to further identify the patients at the greatest risk for postoperative complications is limited; therefore, a better understanding of the mechanisms responsible for major postoperative complications would aid in the design of more targeted and novel prophylactic or therapeutic measures.<sup>[4]</sup>

Surgical injury and postoperative complications may stimulate cytokine production in the early postoperative period, leading to the development of systemic inflammatory response syndrome. These changes in the immune system can be monitored by measuring the cytokines or the inflammatory mediator concentrations in the serum.<sup>[5]</sup> This prospective study was designed to explore the association of systemic inflammation and risk for postoperative complications in patients undergoing general thoracic surgery. The aim of this study was to evaluate the levels of procalcitonin (PCT), interleukin-6 (IL-6) (Invitrogen Corporation, Carlsbad, California, USA), and tumor necrosis factor-alpha (TNF- $\alpha$ ) (Invitrogen Corporation, Carlsbad, California, USA) as early markers of subsequent postoperative complications after major thoracic surgery.

## PATIENTS AND METHODS

Thirty-seven patients (23 males, 14 females; mean age 53.9 years; range 44 to 72 years) undergoing thoracotomies for lung resection at the Department of Thoracic Surgery of Konya Training and Research

Hospital were enrolled in this prospective study. Local ethics committee approval was obtained, and all patients gave written informed consent to participate in the study. Only those patients who were 75 years old or older and who were scheduled to have elective lobectomies for benign or malignant diseases were included in the study. Patients with a history of severe heart disease or hepatic or renal failure, those with American Society of Anesthesiology (ASA) class IV or higher disease, or those undergoing resection of the pleura or chest wall were excluded from the study. In addition, patients on corticosteroids and those with inflammatory findings before a thoracotomy, including a white blood cell count  $>10 \times 10^9/l$  were also not included.

All patients underwent a posterolateral thoracotomy through the fifth intercostal space with an incision from the midscapular to the anterior axillary line. Their demographic information, reasons for the thoracotomy, type of lung resection, operation time, length of hospital stay, and postoperative complications were recorded and are shown in Table 1.

The serum PCT, TNF- $\alpha$ , and IL-6 levels were evaluated preoperatively and on postoperative days one, five, and seven. Peripheral venous blood samples for each patient were collected into blood collection tubes (Vacuette, Greiner Bio-One, Baden-Württemberg, Germany) and centrifuged at 4.500 rpm for 10 minutes (Eppendorf Centrifuge 5702, Eppendorf AG, Hamburg, Germany). Sera samples were then obtained, and the PCT (ng/mL), IL-6 (pg/mL), and TNF- $\alpha$  (pg/mL) levels in the sera were evaluated. An electrochemiluminescence immunoassay (reactive: Elecsys BRAHMS PCT, Roche Diagnostics, Mannheim, Germany; device: Roche cobas e 411, Roche Diagnostics, Mannheim, Germany), was used to analyze the PCT levels. The IL-6 and TNF- $\alpha$  levels were evaluated using enzyme-linked immunosorbent assay (ELISA) (Tecan Minilyser, Tecan Group Ltd.,

**Table 1. Clinical data of patients with and without postoperative complications**

	With POC (n=6)		Without POC (n=31)		p
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	
Gender					
Male	2		22		NS
Female	4		9		NS
Age (years)		66.3 $\pm$ 6.0		53.7 $\pm$ 9.3	0.003
Upper lobectomy/lower lobectomy	4/2		13/18		NS
Operation time (min)		186.7 $\pm$ 19.7		142.1 $\pm$ 22.8	0.001
Malignant/benign disease	5/1		17/14		NS
Hospital stay (days)		12.3 $\pm$ 2.5		7.6 $\pm$ 2.0	0.000

POC: Postoperative complications; SD: Standard deviation; NS: Not significant.

Mannedorf, Switzerland). For the IL-6 and TNF- $\alpha$  measurements, the optical density was measured at 450 nm.

**Statistical analysis**

The serum PCT, TNF- $\alpha$ , and IL-6 levels at each time point were calculated. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 15.0 software program. The Wilcoxon test with Bonferroni correction was used to evaluate the difference between preoperative and postoperative cytokine concentrations. The differences between the groups of patients with and without postoperative complications were analyzed with the Student’s t-test. A p-value of less than 0.05 was considered to be statistically significant.

**RESULTS**

The serum PCT, IL-6, and TNF- $\alpha$  levels before surgery and at postoperative days one, five, and seven are shown in Figure 1. These levels were postoperatively higher in all patients, and they peaked on postoperative day one. This was followed by a decrease until day seven in all patients. The postoperative levels of PCT and IL-6 at all three days were significantly higher compared with the preoperative values ( $p < 0.05$ ), and the postoperative TNF- $\alpha$  levels on day one and five were significantly higher ( $p < 0.05$ ) compared with their preoperative equivalents.

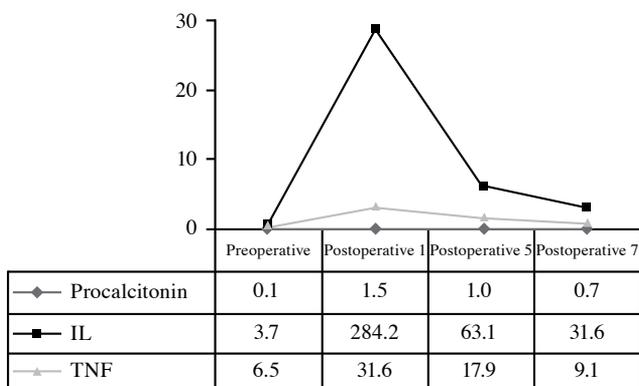
There was no significant difference regarding the baseline levels of the cytokines between patients with and without postoperative complications. Those with postoperative complications had approximately a three-fold elevation in their PCT levels at postoperative days one and five and a two-fold elevation in their IL-6 levels at postoperative day seven. The IL-6 levels on

postoperative day seven were significantly different between the two groups of patients ( $p < 0.05$ ), and the PCT levels on postoperative day one and five also had a significant variance ( $p < 0.05$ ). Changes in the PCT, IL-6, and TNF- $\alpha$  concentrations in patients with and without postoperative complications are showed in Figures 2, 3, and 4.

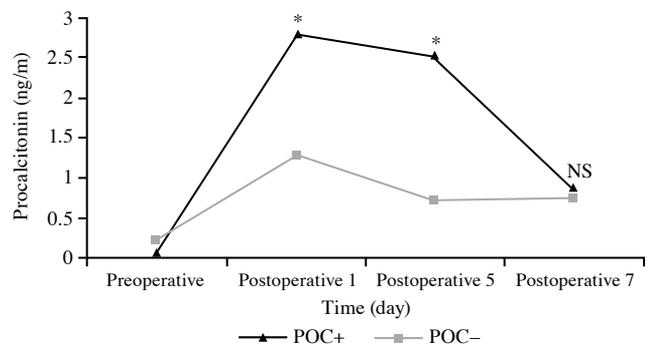
Postoperative complications occurred in six patients (16.2%). One required wound revision due to a wound infection 10 days after the surgery, and one patient who was readmitted with fever and recurrent pleural effusion was treated conservatively. Two patients had persistent air leaks 10 days after surgery, and they were discharged with a Heimlich valve. Two patients experienced postoperative pneumonia defined by fever, cough, and the presence of infiltrates on a chest roentgenogram, and they were treated with a course of antibiotics. One of these patients developed atelectasis, which was treated with pulmonary rehabilitation and bronchoscopic aspiration.

**DISCUSSION**

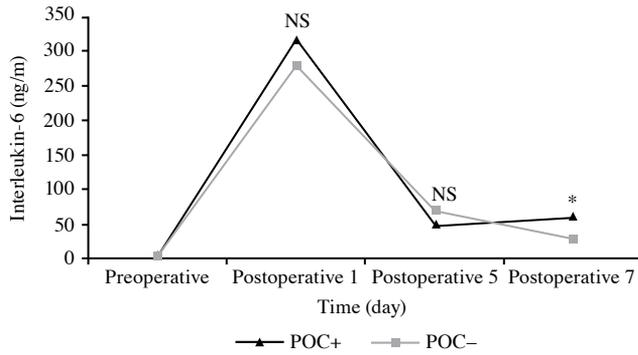
Neuroendocrine, circulatory, and metabolic indices are known to be important indicators of surgical stress, and inflammatory response has also been evaluated as an additional marker.<sup>[6]</sup> A thoracotomy for lung resection represents a major surgical stress and is associated with a significant increase in the circulating levels of inflammatory markers after surgery.<sup>[7]</sup> Polymorphonuclear leukocytes, acute phase reactants, and inflammatory cytokines act as reliable markers of this surgical stress.<sup>[8]</sup> In our study that examined patients undergoing a thoracotomy for lung resection, the PCT, IL-6, and TNF- $\alpha$  levels were significantly elevated in all patients after surgery when compared with their preoperative levels. This may suggest the strong impact



**Figure 1.** Serum procalcitonin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) levels before surgery and at postoperative days 1, 5, and 7.



**Figure 2.** Changes in serum concentrations of procalcitonin (ng/ml, median) in patients without and with postoperative complications. POC+: With postoperative complications; POC-: Without postoperative complications; \*  $p < 0.05$ ; NS: Not significant.



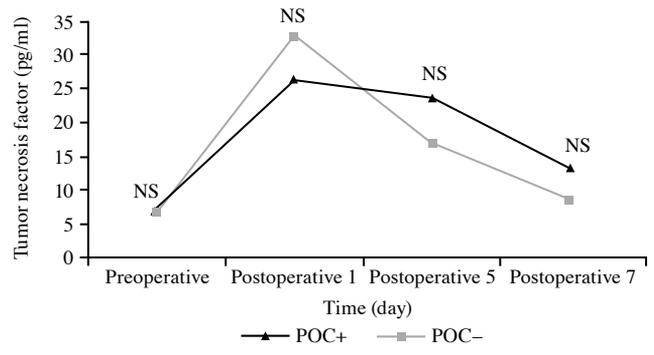
**Figure 3.** Changes in serum concentrations of IL-6 (ng/ml, median) in patients without and with postoperative complications. POC+: With postoperative complications; POC-: Without postoperative complications; \* p<0.05, NS: Not significant.

that operative injuries have on the release of these mediators.

Patients undergoing major surgical resection for malignant or benign disease are at high risk for postoperative complications. Early identification of these patients may enable the selection of those who may benefit from early intensive management. Furthermore, early diagnosis and treatment of postoperative complications may greatly improve outcome. In our study, the serum levels of IL-6 (on postoperative day 7) and PCT (on postoperative days 1 and 5) were significantly higher in patients with postoperative complications. Our results suggest that measuring PCT levels may be useful for the early diagnosis of postoperative complications following major thoracic surgery.

The elevated levels of cytokines in patients with postoperative complications after major surgery gave rise to the idea that some of them could serve as early markers of these complications. This could subsequently lead to a more rapid administration of appropriate treatment that might decrease the morbidity and mortality rates.<sup>[9,10]</sup> Similar to our study, Szczesny et al.<sup>[5]</sup> showed that the serum levels of IL-6 on postoperative day seven were significantly higher in patients with postoperative complications when compared with those without complications. Additionally, Mokart et al.<sup>[9]</sup> showed that IL-6 is a good independent early marker of postoperative sepsis, severe sepsis, or septic shock after major oncological surgery. Although cytokines like IL-6 have been shown to be associated with the severity of sepsis and patient outcome, they are not yet established tools to be used for diagnosis and clinical decision-making.<sup>[11,12]</sup>

Procalcitonin measurements could be helpful in the early diagnosis of postoperative infection after major surgery.<sup>[13]</sup> This peptide precursor of the hormone



**Figure 4.** Changes in serum concentrations of TNF- $\alpha$  (pg/ml, median) in patients without and with postoperative complications. POC+: With postoperative complications; POC-: Without postoperative complications; \* p<0.05; NS: Not significant.

calcitonin is known to be an early marker of severe sepsis,<sup>[14]</sup> but it has been correlated with the severity of systemic inflammatory response syndrome after severe trauma<sup>[15,16]</sup> and so may be distorted by major surgery.<sup>[17]</sup> In our study, the serum level of PCT on postoperative day one was significantly higher in patients with postoperative complications versus those without complications. Except for two patients who had persistent air leaks, all of the complications after surgery in our patients were associated with infection, and the early elevation of PCT levels in patients with postoperative complications was attributed to this fact. Reith et al.<sup>[13]</sup> studied the prognostic predictive value of elevated PCT levels in 70 patients undergoing elective colorectal surgery and aortic surgery. An increase of PCT levels >1.0 ng/ml the day after surgery was closely related to postoperative complications such as pneumonia or anastomotic leak. These results are also similar to those of Harbarth et al.<sup>[14]</sup> who differentiated non-septic systemic inflammatory response syndrome from sepsis, using the same PCT cut-off value, in newly admitted ICU patients.

Szczesny et al.<sup>[5]</sup> suggested that the elevated concentration of IL-6 in serum is a good early marker of the severity of surgical injury and reflects the development of postoperative complications. Amar et al.<sup>[4]</sup> suggested that C-reactive protein (CRP) and IL-6 can help identify patients who are at high risk for major cardiopulmonary complications after general thoracic surgery. A study dealing exclusively with thoracic surgery was published in 2005 by Falcoz et al.<sup>[18]</sup> In this trial, the PCT levels were significantly higher in patients with postoperative infection than in patients with no postoperative infection. The authors found that PCT can provide accurate information about the postoperative course and that pathological values are detected before the occurrence of clinical infection.

The results of our study are promising and should be confirmed in a larger population of patients who plan to undergo lung cancer surgery before introducing this test into routine clinical practice.

In conclusion, patients who undergo major thoracic surgery are at high risk for postoperative complications. An elevated PCT level on postoperative day one is a promising early indicator of postoperative complications. In addition, we found that elevated concentrations of PCT, IL-6, and TNF- $\alpha$  in the postoperative period are markers of the severity of surgical injury. As a result, early diagnosis may greatly improve patient outcome.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

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